(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 May 2001 (03.05.2001)

PCT

(10) International Publication Number
WO 01/30405 A1

(51) International Patent Classification[7]: A61L 15/32

(21) International Application Number: PCT/GB00/04157

(22) International Filing Date: 27 October 2000 (27.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9925380.9 28 October 1999 (28.10.1999) GB

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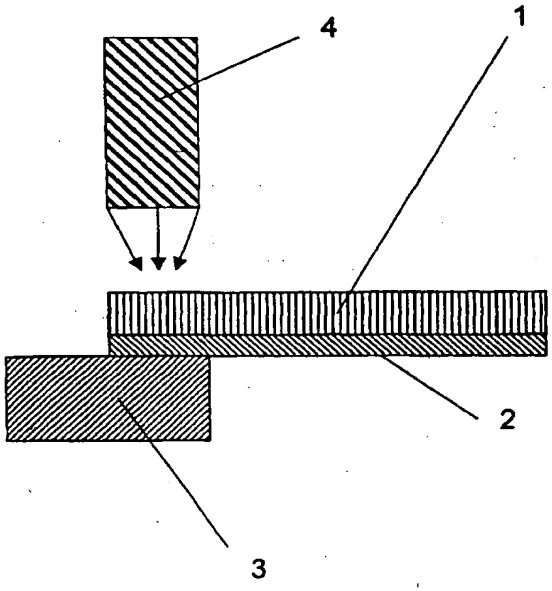
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FLEXIBLE SHEETS FOR USE IN THERAPY



(57) Abstract: A sheet suitable for use in therapy and comprises a material suitable for therapeutic use by topical administration. The sheet is flexible, hydratable and activatable so that it bonds to tissue whilst retaining its integrity, and bears on at least one side thereof a layer of liquid tissue bonding material. Preferably, the sheet itself comprises a tissue bonding material, incorporated in a solid matrix. Most preferably, both the sheet and the liquid tissue bonding material comprise albumin.

WO 01/30405 A1

BNSDOCID: <WO___0130405A1_I_>

Title: Flexible sheets for use in therapy

This invention relates to therapeutic materials in the form of sheets suitable for topical administration to either an internal or external organ of the body, the sheets being secured by means of tissue bonding material.

The use of tissue bonding material as an adhesive to bond tissues together after surgery or to repair wounds, eg in place of suturing or the like, is known. Such material commonly comprises proteinaceous material which is applied to the tissues to be joined and then subjected to curing by the action of heat or light. This causes the material to crosslink to itself and to the tissues, thereby creating a bond WO 96/22797 describes such materials which consist substantially of albumin together with a chromophore which changes colour when the end point of the crosslinking process has been reached, thereby preventing the absorption of further energy.

Our co-pending International patent application PCT/GB99/02717 discloses albumin-based sheets which can be applied topically and caused to crosslink and bond to the underlying tissue. Again, the sheet may incorporate a chromophore to indicate when the bonding process is complete. Such sheets are very beneficial but may be insufficiently adhesive for certain applications. In addition, the presence of a chromophore, whilst it performs a very valuable function, may also be accompanied by certain disadvantages in that the chromophore provides no therapeutic benefit but may be toxic for some applications.

It has now been found that particularly beneficial effects can be achieved in certain applications by a combination of the approaches described in the two prior documents referred to above.

Thus, according to the invention there is provided a sheet suitable for use in therapy and comprising a material suitable for therapeutic use by topical administration, the sheet being flexible, hydratable and activatable so that it bonds

to tissue whilst retaining its integrity, said sheet bearing on at least one side thereof a layer of liquid tissue bonding material.

By a "tissue bonding material" is meant a material which when applied to body tissues is capable of binding to those tissues and of causing the tissues to adhere to each other. The mechanism of such adhesion will normally involve curing by which the tissue bonding material molecules covalently bond to each other (cross-linking) and to the tissues.

By "liquid" tissue bonding material is meant a material of sufficient fluidity to be applied to the surface of the sheet. The material is preferably of sufficient viscosity to be retained at the locus to which it is applied. The material may thus be of the nature of a gel.

Most preferably, the sheet itself comprises a tissue bonding material, incorporated in a solid matrix.

The tissue bonding material may be applied over the whole surface of the sheet. Alternatively, the tissue bonding material may be applied to only part of the sheet, eg around the periphery of the sheet. In a further alternative, the tissue bonding material may be applied to the tissue to which the sheet is to be attached, the sheet then being applied to the tissue bonding material.

The invention thus also provides a method of attaching to a tissue a flexible, hydratable and activatable sheet, which method comprises applying to the sheet and/or to the tissue a tissue bonding material and then applying the sheet bearing the tissue bonding material to the tissue or applying the sheet to the tissue bonding material previously applied to the tissue.

Both the sheet and the tissue bonding material applied to it will most commonly comprise a crosslinkable proteinaceous or other peptide material. The material may be selected from natural and synthetic peptides, enzymatically cleaved or shortened variants thereof and crosslinked derivatives thereof, as well as mixtures

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of any of the above. Included among the peptides are structural proteins and serum proteins. Examples of proteins are albumin, α-globulins, β-globulins, γ-globulins, transthyretin, collagen, elastin and fibronectin and coagulation factors including fibrinogen, fibrin and thrombin.

The tissue bonding material may be formulated in any suitable form for application to the sheet or to the tissue to which the sheet is to be applied. For instance, the formulation may be a liquid or low viscosity gel. A certain degree of viscosity may be desirable in order to aid retention of the material at the locus to which it is applied. Viscosity-modifying components which may be incorporated into the composition include hyaluronic acid and salts thereof such as sodium hyaluronate, hydroxypropylmethylcellulose, glycerine, dextrans, honey, sodium condroitin sulphate and mixtures thereof.

The liquid tissue bonding material may be prepared by mixing the various components in appropriate proportions. The tissue bonding material may for example be dispersed or dissolved in water, together with any additional components such as viscosity-modifying agents.

The liquid formulation most preferably also comprises a plasticiser to confer sufficient flexibility on the liquid tissue bonding material after curing. Suitable plasticisers include polyalcohols, eg glycerol, sorbitol etc.

The sheet may comprise a single layer of material. Alternatively, especially where a thin layer is used and/or the material has insufficient integrity for the desired purpose, a carrier layer may be provided. Suitable materials for the carrier layer are biocompatible materials, eg polybutyrate, polysaccharides, polytetrafluoroethylene, polyesters, glycoproteins, polymer composites, collagen (including cross-linked collagen), pericardium, ethacrylate, polyurethane and derivatives thereof. Other materials include absorbable and non-absorbable suture materials, eg polypropylene, polyglactin, polylactic acid, polyglycolic acid, polydioxanone and polyglyconate.

As for liquid tissue bonding material, the sheet formulation preferably further comprises a plasticiser in order to ensure that the sheet has sufficient flexibility, even after polymerisation or cross-linking. Suitable plasticisers include polyalcohols, eg glycerol, sorbitol etc.

The sheet preferably also comprises a synthetic structural polymer to confer strength and elasticity on the sheet. Suitable such polymers include water-soluble thermoplastic polymers, in particular selected from the group consisting of poly(vinyl alcohol), poly(ethylene glycol), poly(vinyl pyrrolidone), poly(acrylic acid), poly(acrylamide), copolymers of methylvinyl ether with maleic anhydride in the anhydride, acid, ester or mixed salt form, and similar materials.

A relatively small proportion of surfactant, most preferably a non-ionic surfactant, will generally be incorporated into the sheet, though normally to facilitate manufacture (prevention of foaming etc) rather than to confer any beneficial property on the finished product. Suitable surfactants include block copolymers of ethylene oxide and propylene oxide, such as those sold under the trade mark Pluronic® by BASF.

The sheet may be manufactured by mixing the different components in aqueous solution as follows:

i) tissue-bonding material: 5 – 80%, more preferably 10 – 60 %, and most preferably 15 to 40%.

ii) structural polymer : 0.01 – 20%, more preferably 1 - 10% , and most preferably 2 – 8%.

iii) surfactant : 0.001 – 10%, more preferably 0.01 – 5%, and most preferably 0.1 – 2%.

iv) plasticiser : 0.01 – 60%, more preferably 1 – 50%, and most preferably 10 – 40%

The sheet may be prepared by casting the above solution into a suitable non-stick mould (e.g. of PTFE), and allowing it to set through evaporation.

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The casting process used to achieve the desired thickness of the sheet may involve pouring, manual spreading or spraying of the component solutions.

For most applications, the sheet according to the invention may be 20 – 200 µm in thickness, and typically approximately 100 µm in thickness.

The sheet will typically contain between 10% and 50% water by weight, and most preferably between 20% and 40%. The sheet may be partially or totally hydrated with a suitable aqueous medium at or following implantation (eg a body fluid or saline solution).

The preferred material for use in the present invention, both for the sheet and the tissue bonding material, is a soluble protein which is not part of the clotting cascade. Porcine albumin or porcine pericardium or any abundant non-thrombogenic protein, ie excluding collagen, may be used. Genetically or chemically modified versions of such proteins may also be suitable. Albumin is particularly suitable because of its chemical and physical properties.

Particularly preferred formulations of both the sheet and the liquid tissue bonding material are formulations comprising albumin. Mammalian albumin is preferred, particularly porcine albumin. The formulations most preferably further comprise glycerol as plasticiser.

The tissue bonding material may, or may not, contain a thermochromic compound (which undergoes a colour change on the application of heat) and/or a photochromic compound (which undergoes a colour change on the application of light). For example, the material may include a chromophore, such as methylene blue, which will change colour when the end point (when light activated) has been reached, as described in WO 96/22797. Such a visual colour change may provide the user with an indication that sufficient energy has been applied to ensure that curing of the tissue bonding material has occurred. In addition, when curing is

complete the resultant colour change ensures that the material will absorb no further radiant energy. This provides protection against excess energy input.

If a light activated chromophore is present it provides the user, ie normally a surgeon or veterinary surgeon, with means to determine whether or not adequate energy has been provided in the desired area, thereby preventing thermal damage as a result of the application of excessive energy.

The sheet may also contain a thermochromic compound and/or a photochromic compound. The sheet preferably readily transmits energy applied to it to the coating of tissue bonding material. Thus, where light energy is to be applied the sheet is preferably at least substantially transparent, at least at the relevant wavelengths.

Amongst the applications in which the sheet and method of the invention may be used are the following:

Targeted/Sustained Drug Delivery

Therapeutic agents may be incorporated into the sheet, either by simple mixing during manufacturing or by covalent bonding to the materials making up the sheet. The sheet may be applied to a specific tissue (eg a tumour) in a simple surgical procedure. The therapeutic agents will be released from the sheet as it degrades.

The rate at which the therapeutic agents are released may depend on the rate at which the sheet degrades and this in turn may be controlled by, for instance, adjusting the degree of crosslinking during the manufacturing process.

Arterial Puncture Repair

The sheet may be applied externally to close an arterial puncture made for any one of a number of purposes.

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Bladder/GI Repair

A sheet according to the invention may be applied to the surface of the bladder or part of the gastrointestinal tract in order to effect a repair. Alternatively, such a sheet may be applied to a graft or the like which is applied to those tissues. This may increase the strength of the graft, reduce porosity and provide a biocompatible and anti-thrombogenic surface.

Wound Healing

The sheet according to the invention may be used as a form of dressing applied to the external surface of the skin to promote wound healing. Once the sheet begins to degrade fibroblasts will move in and begin to deposit components of the extra cellular matrix. Furthermore, factors such as growth factors and cAMP, which are known to promote the proliferation of skin cells, may be incorporated into the sheet to further assist in the healing process.

Skin Closure

The sheets according to the invention may be applied topically to promote wound closure, eg as an alternative to sutures. This may have beneficial effects in that it may reduce scarring, and may therefore be useful for cosmetic purposes during minor surgery.

Hernia Repair

The sheet according to the invention may be used to provide additional support during the reinforcement of hernia repair procedures. It may be used on its own, or alternatively attached to an external mesh or support.

The invention will now be described in greater detail, for illustrative purposes only, with reference to the following Examples and to Figure 1 which shows schematically the manner in which the sheet according to the invention is used..

Example 1 – Sheet Formulation

0.9g porcine albumin was dissolved in 3.0ml water for injection. To this solution 0.585g sorbitol was added and dissolved. The solution was then heated 50□C, left to cool for thirty minutes and then cast on a level PTFE-coated surface.

The sheet so formed is cut into discs, eg of diameter 30mm, or into square or rectangular patches of similar dimension.

Tissue adhesive such as described in Example 2 below may then be applied to one surface of the patches, either over the whole surface or in a band around the periphery.

Example 2 – Liquid Tissue Bonding Material

Porcine albumin	41% w/w
Methylene blue	0.24% w/w
Glycerol	2% w/w
Water for injection	q.s.

The composition was made up by dissolving/dispersing the albumin, methylene blue and glycerol in the water for injection.

Figure 1 shows schematically the manner in which a sheet prepared in accordance with Example 1 and coated on one side with the adhesive of Example 2 is applied to a tissue. As can be seen, the side of the sheet 1 with the coating of adhesive 2 is applied to the tissue 3. There is an immediate limited degree of adhesion which is sufficient to retain the sheet 1 in place. Full adhesion is then brought about by the application to the sheet of intense polychromatic light via a pencil-like handpiece 4 held by the surgeon. The handpiece 4 is connected by suitable means, eg an optical fibre (not shown), to a remote light source unit.

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Light from the handpiece 4 passes through the substantially transparent sheet 1 and is absorbed by the methylene blue in the adhesive coating 2 and dissipated within that coating as heat energy. This heat energy initiates crosslinking of the albumin molecules in the adhesive coating layer 2, to themselves and to the sheet 1 and the tissue 3. Once full crosslinking has occurred the methylene blue loses its blue colour, providing the surgeon with a visual indication of the completeness of the activation.

Further examples of sheet formulations to which the gel formulation of Example 2 may be applied are the following:

Example 3

1.51g of porcine albumin, 0.1g of 80% hydrolysed polyvinyl alcohol, 1.42g of glycerol and 0.01g of Pluronic 25R2 were dissolved in 2.02g of water for injection. 0.1 ml of this solution was poured onto a level PTFE surface, and spread to a thickness of approximately 50µm. The solution was heated to 120°C for 10 minutes to evaporate off water and allowed to cool.

Example 4

3.03g of porcine albumin, 0.5g of 80% hydrolysed polyvinyl alcohol, 3.00g of glycerol and 0.02g of Pluronic 25R2 were dissolved in 3.53g of water for injection. 0.1 ml of this solution was poured onto a level PTFE surface, and spread to approximately 30µm thick. The matrix was heated at 120°C for 20 minutes and allowed to cool.

Example 5

9.00g of porcine albumin, 1.53g of 80% hydrolysed polyvinyl alcohol, 8.98g of glycerol and 0.06g of Pluronic 25R2 were dissolved in 10.56g of water for injection. 0.3 ml of this solution was poured onto a level PTFE surface, and

spread to a thickness of approximately 50µm, and left at room temperature for 1 hour.

Claims

1. A sheet suitable for use in therapy and comprising a material suitable for therapeutic use by topical administration, the sheet being flexible, hydratable and activatable so that it bonds to tissue whilst retaining its integrity, said sheet bearing on at least one side thereof a layer of liquid tissue bonding material.

2. A sheet as claimed in Claim 1, wherein the sheet comprises a tissue bonding material, incorporated in a solid matrix.

3. A sheet as claimed in Claim 1 or Claim 2, wherein the liquid tissue bonding material is applied over the whole surface of the sheet.

4. A sheet as claimed in Claim 1 or Claim 2, wherein the liquid tissue bonding material is applied only around the periphery of the sheet.

5. A sheet as claimed in any preceding claim, wherein the sheet and the liquid tissue bonding material applied to it comprise a crosslinkable proteinaceous or other peptide material.

6. A sheet as claimed in Claim 5, wherein said material is selected from natural and synthetic peptides, enzymatically cleaved or shortened variants thereof and crosslinked derivatives thereof, and mixtures of any thereof.

7. A sheet as claimed in any preceding claim, wherein the liquid tissue bonding material includes a viscosity modifying agent.

8. A sheet as claimed in any preceding claim, wherein the liquid tissue bonding material comprises a plasticiser.

9. A sheet as claimed in Claim 8, wherein the plasticiser is a polyalcohol.

10. A sheet as claimed in any preceding claim, wherein the sheet is provided with a biocompatible carrier layer of a material selected from polybutyrate, polysaccharides, polytetrafluoroethylene, polyesters, glycoproteins, polymer composites, collagen (including cross-linked collagen), pericardium, ethacrylate, polyurethane and derivatives thereof.

11. A sheet as claimed in any preceding claim, wherein the sheet comprises a plasticiser.

12. A sheet as claimed in Claim 11, wherein the plasticiser is a polyalcohol.

13. A sheet as claimed in any preceding claim, wherein the sheet further comprises a synthetic structural polymer selected from the group consisting of poly(vinyl alcohol), poly(ethylene glycol), poly(vinyl pyrrolidone), poly(acrylic acid), poly(acrylamide), and copolymers of methylvinyl ether with maleic anhydride in the anhydride, acid, ester or mixed salt form.

14. A sheet as claimed in any preceding claim, wherein the sheet has a thickness of 20 – 200 μm.

15. A sheet as claimed in any preceding claim, wherein the sheet contains between 10% and 50% water by weight.

16. A sheet as claimed in any preceding claim, which comprises albumin.

17. A sheet as claimed in Claim 16, wherein said albumin is porcine albumin.

18. A sheet as claimed in Claim 16 or Claim 17, wherein both the sheet and the liquid tissue bonding material comprise albumin.

19. A sheet as claimed in any preceding claim, wherein the liquid tissue bonding material comprises a thermochromic compound (which undergoes a

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colour change on the application of heat) and/or a photochromic compound (which undergoes a colour change on the application of light).

20. A sheet as claimed in Claim 19, which comprises methylene blue.

21. A method of attaching to a tissue a flexible, hydratable and activatable sheet, which method comprises applying to the sheet and/or to the tissue a liquid tissue bonding material and then applying the sheet bearing the tissue bonding material to the tissue or applying the sheet to the tissue bonding material previously applied to the tissue.

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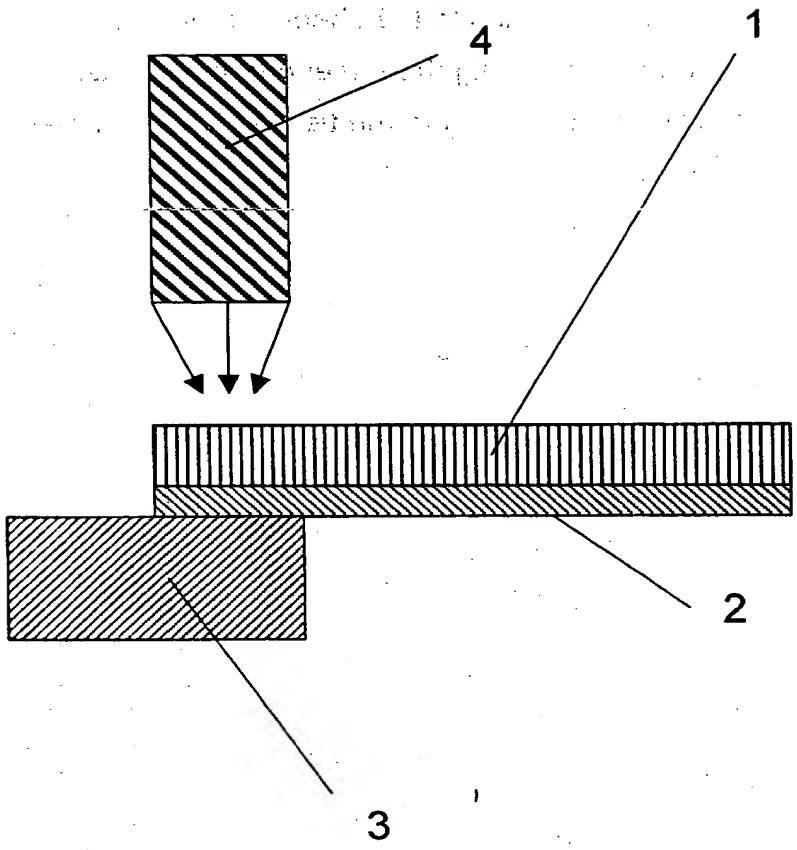
Figure 1



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INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/GB 00/04157

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 14513 A (INTERFACE BIOMEDICAL LAB CORP) 3 September 1992 (1992-09-03) page 3, line 22 - line 36 page 9, line 3 - line 33 page 15, line 31 -page 16, line 1 ---	1-21
P,X	WO 00 10618 A (DAVIES GWILYM ALBAN; WILKINSON FRANCIS (GB); TISSUEMED LTD (GB)) 2 March 2000 (2000-03-02) page 6, line 13 - line 15 claims 1-5 ---	1-21
A	US 5 791 352 A (DAPPER GREG ET AL) 11 August 1998 (1998-08-11) column 2, line 34 - line 62 claims 1,7,8,10-12 --- -/--	1,2,5,6, 8,9, 11-16,21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

°Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2001	21/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Heck, G

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/GB 00/04157

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 292 362 A (EATON ALEXANDER M ET AL) 8 March 1994 (1994-03-08) claims 39,40	1,2,5,6, 19-21

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

3NSDOCID: <WO___0130405A1_I_>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

information on patent family members

Int. onal Application No
PCT/GB 00/04157

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